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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,451	KHOSLA ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1-4,8-11 and 19-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-7 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/19/02, 9/30/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on January 21, 2004), Applicants filed an election received on February 17, 2004. Claims 1-25 are pending in the instant Office action.

Election

2. Applicant's election without traverse of Group IV, Claims 5-7 and 12-18, in a paper received on February 17, 2004 is acknowledged. Claims 1-25 are pending in the instant application. Claims 1-4, 8-11, and 19-25 are withdrawn from consideration as non-elected inventions. Claims 5-7 and 12-18 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for 09/798,033 filed on February 28, 2001; said application discloses the claimed invention. The instant application is also granted the benefit of priority for 09/687,855 filed on October 13, 2000, which claims priority to provisional applications 60/159,090, 60/203,082, and 60/232,379 filed on October 13, 1999, May 18, 2000, and September 14, 2000, respectively. The instant application is also granted the benefit of priority for 60/355,211 filed on February 8, 2002.

Information Disclosure Statement

4. The information disclosure statements filed on June 19, 2002 and September 30, 2002 have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies.

Declaration

5. The Examiner notes that the declaration filed on June 25, 2002 is valid for the instant application and that priority claims to U.S. applications 09/798,033 and 09/687,855 incorrect note said applications as patented while they are still pending. No correction is required.

Compliance with the Sequence Rules

6. The instant application fully complies with the sequence rules by virtue of the sequence listing filed on June 25, 2002.

Objections to the Specification

7. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01).

8. The specification is objected to for having confusing "related application" information in the first paragraph. The notation to attorney docket number 286003022600 must be replaced by the appropriate provisional application number 60/355,211 as noted in the declaration filed on June 25, 2002. Correction is required.

9. The specification is objected to for the following informalities:

a) Lacking updated references to patent applications that have been granted as patents. Occurrences in paragraphs [0031], [0032], [0070], [0071], [0083], [0095], [0104].
b) The notation of "US/96/11317" in [0092] is confusing; while it seems to be an international application, this is not a complete number.
c) In [0105], updating of the submitted Admiraal article with a complete citation is required.
d) In [0185], reference to Figure 4 seems to be incorrect; it should be Figure 5. Correction or clarification is required.

10. The specification is objected to for not having a clear Brief Description of the Drawings. On pages 7-8, references to Figure 2 must describe Figures 2A and 2B (see first line of [0021]). Similarly for Figure 5. For Figure 7, either each of 7A, 7B, and 7C should get their own paragraph or they should be described all together in the first line of [0023]. Clarification is required.

Claim Objections

11. Claims 5-7 and 12-18 are objected to for pending from a non-elected claim, Claim 4. Correction is required, for example by incorporating all the limitations from Claim 4 into Claim 5.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 5-7 and 12-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "enhanced" is unclear. No original level has been

defined that could be enhanced. Clarification is required. The Examiner suggests deleting the term "enhanced" for clarity.

13. Claims 5-7 and 12-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The nature of the A-T didomain in the host cells claimed is unclear. Reference to Claim 4 could mean the rifamycin A-T didomain or could mean any A-T didomain that is primed by a substituted benzoate since Claim 4, itself is unclear in the nature of its method steps and what products they utilize. Moreover, it is unclear if the holo A-T didomain is intended as well. Clarification on all these points is required.

14. Claims 6-7 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "modified" polyketide at the end of the claims is unclear. Modified with respect to what, rifamycin only? Any known polyketide? Clarification is required. The Examiner suggests deleting the term "modified" for clarity.

15. Claims 14-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "a complete polyketide derived from" with respect to the polyketides named is unclear. First, the nature of a "complete" polyketide is unclear. Second, consider for example, the difference between erythromycin and oleandomycin being only a methyl group; what are the metes and bounds of a derived polyketide? Clarification is required.

Additionally, for Claims 15 and 16, the limitation of a "modified rifamycin" is unclear since the amount of modification is not specified. Moreover, the term "a 6-dEB analog" is unclear since so many polyketide are related and the definition of "analog" is also unclear. Clarification on these points is required.

16. Claims 14-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Based on the specification, it is clear that the invention involved making hybrid polyketide synthase gene clusters that use the promiscuous rifamycin A-T didomain as a loading module for extender modules of PKSs. While claims 14-17 describe making polyketide derivatives and/or using PKS expression systems, such a hybrid is not a limitation in the claims. Particularly for Claim 17, the lack of a hybrid is confusing since no A-T didomain loading module is know to be a separate protein, thus, the expression system of the PKS should include a hybrid with the A-T didomain. For all these reasons, the instant claims are not clear.

17. Claim 16 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The abbreviation "6-dEB" must be defined upon its first appearance in the claims for clarity. Clarification is required.

The Examiner also notes that the abbreviation "A-T-didomain" is used in Claim 5 and defined in the non-elected claim 4. If Applicant is incorporating Claim 4 into Claim 5, the definition of the abbreviation should also be used in Claim 5.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 5-7 and 12-18 are rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are directed to host cells comprising an expression system for an A-T didomain wherein the didomain is primed by substituted benzoates. While the art defines the structure and function of a didomain adequately for the purposes of written description, those didomains, which utilize substituted benzoates, as a subgenus of all didomains, is not described either in the specification or the art.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

In the specification, several examples of A-T didomains are disclosed as being from rifamycin, rapamycin, ansatrienin, microcystin, and pimaricin (see page 19). Only a single example of these has been shown to utilize substituted benzoates, that is the didomain from rifamycin. No examples of other substituted benzoate didomains are described. The instant claims are drawn to a *subgenus* of all didomains genes within the structural limitations (as

known in the art), wherein the didomain must utilize a substituted benzoate. The specification does not describe all didomains to the exclusion of didomains that utilize substituted benzoates. Thus, the claimed subgenus does not have adequate written description.

19. Claims 5-7 and 12-18 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for host cells that produce polyketides comprising an A-T didomain expression system and an sfp expression system (or another proven means of phosphopantetheinylating the didomain, such as in a polyketide producing host cell), does not reasonably provide enablement for host cells, such as *E. coli* without the sfp expression system. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To make such host cells in the absence of sfp would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In example 6 of the instant specification, apo and holo A-T didomains are contrasted, wherein the holo didomain has interacted with the phosphopantetheinyl transferase enzyme, sfp, and wherein the apo form in inactivate and the holo for is active. Thus, to produce polyketides, clearly the holo form is required, and to produce the holo form, sfp is required. The specification provides no guidance or working example for the production of polyketides in the absence of said sfp. The state of the art is that little information about priming PKS loading domains is known that is specific for domains other than typical loading domains, such as that found in DEBS. Thus, the predictability of being able to produce a polyketide in the absence of sfp is very low. Therefore, the instant claims are not enabled to the full extent of their scope.

20. Claims 6-7 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for host cells containing didomains that utilize particularly substituted benzoates, does not reasonably provide enablement for host cells containing didomains that utilize all substituted benzoates, particularly 4-substituted and 2,3-substituted. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To make such host cells that utilize 4-substituted and 2,3-substituted benzoates would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

The instant specification tests a variety of substituted benzoates for their ability to prime rifamycin A-T didomain (see page 55, Table 1). None of the examples include 4-substituted or 2,3-substituted benzoates. While the rifamycin A-T didomain is considered to be a flexible enzyme, the nature of enzyme reactions require a specific fit between within the catalytic site of the enzyme as well as a particular electronic make-up of the substrate to be susceptible to catalytic reaction. In both 4-substituted and 2,3-substituted benzoates, these factors are not tested and cannot be assumed to be productive based on the evidence presented in the specification. The ability of rifamycin A-T didomain to use these substrates is wholly unpredictable. Thus, the claims are not enabled to the full extent of their scope.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

KK 4/28/04

21. Claims 5-7, 15 and 17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hu *et al.* (A host-vector system for analysis and manipulation of rifamycin polyketide biosynthesis

in Amycolatopsis mediterranei. Microbiology (1999) 145: 2335-2341). The instant claims are drawn to prokaryotic host cells modified to contain an expression system for an A-T didomain, which primes a substituted benzoate such as 3-amino-5-hydroxybenzoate, and a polyketide synthase, wherein the host cells, previously unable to produce polyketides, now produces a modified rifamycin polyketide.

Hu *et al.* teach inserting "rifA, which encodes AHBA-CoA ligase and the first three modules of the rifamycin PKS" (see legend of Figure 4) into a mutant of *A. mediterranei* which does not normally produce polyketides (see pages 2338-2339, bridging paragraph). The AHBA-CoA ligase of rifamycin inherently primes a variety of substituted benzoates. This transformant produces polyketide products desamino P8/1-OG and P8/1-OG, which are rifamycin precursors (see Figure 4 and page 2339).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 5-7, 12, 14, 16, and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Marsden *et al.* (Engineering Broader Specificity into an Antibiotic-Producing Polyketide Synthase. Science (1998) 279: 199-202) in view of Floss *et al.* (see IDS). The instant claims are drawn to *Streptomyces* host cells modified to contain an expression system for an A-T didomain, which primes a substituted benzoate such as 3-amino-5-hydroxybenzoate, and

a polyketide synthase, wherein the host cells, previously unable to produce polyketides, now produces a erythromycin analog.

Marsden *et al.* teach using the promiscuous avermectin loading domain in place of the native erythromycin loading domain to produce erythromycin analogs in *Streptomyces coelicolor* CH999 cells, which natively do not produce polyketides, by transforming CH999 cells with a hybrid gene cluster comprising the avermectin loading domain and modules 1-6 of the DEBS PKS (see Figure 1B). Marsden *et al.* do not teach using other promiscuous loading domains.

Floss *et al.* teach that the loading domain of rifamycin is promiscuous and that the tolerance of variability downstream in polyketide processing in DEBS is high 9see page 594, right column).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the above teachings and produce the claimed invention of a CH999 host cell containing a hybrid PKS of the rifamycin loading domain and the DEBS PKS, minus the loading domain, because variability in starter unit leads to variability in polyketide product, which is desirable, as clearly taught in Marsden *et al.* It would have been obvious to combine the teachings because such a combination is clearly indicated by Floss *et al.* and the express reasoning behind the experiments of Marsden *et al.* is to attain variability in the starter unit. One would have had a reasonable expectation of success that such a hybrid PKS would yield erythromycin analogs due to the combinatorial abilities of PKSs and NRPSs that is well known in the art.

23. Claims 13 and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Marsden *et al.* (see above) in view of Floss *et al.* (see IDS) and Barr *et al.* (USPN 6,033,883, see IDS). The instant claims are drawn to *E. coli* host cells modified to contain an expression system for (1) an A-T didomain, which primes a substituted benzoate such as 3-amino-5-hydroxybenzoate, (2) a polyketide synthase, wherein the host cells, previously unable to produce polyketides, now produces a erythromycin analog, and (3) a phosphopantetheinyl transferase.

Marsden *et al.* and Floss *et al.* teach as describe above. These teachings use a *Streptomyces* host cell, which does not require additional machinery for the phosphopantetheinylation of the loading domain required prior to priming. Marsden *et al.* and Floss *et al.* do not teach the use of *E. coli* host cells with an additional expression system for a phosphopantetheinylating enzyme.

Barr *et al.* teach the expression of hybrid PKS gene clusters in *E. coli* with the co-expression of a phosphopantetheinylating enzyme, such as *sfp* from *B. subtilis*, due to the ease of manipulation of *E. coli* (see columns 4-6).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the above teachings to produce the modified *E. coli* host cells for the production of novel erythromycin polyketides for the reasons stated above for the combination of Marsden *et al.* and Floss *et al.* as well as because *E. coli* is a microbial system which is easily grown and manipulated. One would have been motivated to combine all of the above teachings for the reasons stated above for the combination of Marsden *et al.* and Floss *et al.* and because the ease of growth and manipulation of *E. coli* is desirous for potential therapeutics, such as erythromycin

analogs. One would have had a reasonable expectation of success in the above combination because other hybrid polyketides are produced in the system of Barr *et al*.

Other Relevant Art

24. The following are cited to complete the record:

a) Katz *et al*. (USPN 6,063,561) teach a hybrid of the rapamycin ligase with the DEBS gene cluster (minus its native loading domain), which produces an erythromycin analog in *S. erythraea*; rapamycin ligase primes with a substituted cyclohexencarboxylic acid (a shikimate), not a substituted benzoate (see Aparicio *et al*. Organization of the biosynthetic gene cluster for rapamycin in *Streptomyces* hygroscopicus: analysis of the enzymatic domains in the modular polyketide synthase. Gene (1996) 169: 9-16).
b) Keating *et al*. (Selectivity of the Yersiniabactin Synthetase Adenylation Domain in the Two-Step Process of Amino Acid Activation and Transfer to a Holo-Carrier Domain. Biochemistry (2000) 39: 2297-2306) teach the A-T didomain of the NRPS of *Y. pestis*; it does not use a substituted benzoate nor does it produce a polyketide.
c) Chen *et al*. (Epothilone biosynthesis: assembly of the methylthiazolylcarboxy starter unit on the EpoB subunit. Chemistry & Biology (Sept., 2001) 8: 899-912) the priming of the epotihlone loading domain, an A-T didomain, and its expression in *E. coli* along with a phosphopantetheinyl transferase, sfp; it does not use a substituted benzoate.

Conclusion

25. Claims 5-7 and 12-18 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Examiner
Art Unit 1652

April 28, 2004